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EXAMINER	
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ART UNIT	PAPER NUMBER
1642	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PTO-PAT-Email@rfem.com

Office Action Summary	Application No.	Applicant(s)	
	10/003,463	MOLINA ET AL.	
	Examiner	Art Unit	
	Laura B. Goddard, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-13 and 21-29* is/are pending in the application.

4a) Of the above claim(s) *12,13 and 21-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-11 and 27-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 3, 2007 has been entered.

2. Claims 1, 3-13, and 21-29 are pending. Claim 29 is new. Claims 1, 3, 8, and 28 are amended. Claims 21-26 remain withdrawn as being drawn to a non-elected invention. Claims 12 and 13 remain withdrawn as being drawn to a non-elected species. Claims 1, 3-11 and 27-29, as drawn to the elected species of polypeptide antigen, wherein the antigen is HER-1, and oily adjuvant, are currently under prosecution.

Priority/Oath/Declaration

3. This application claims priority to and Applicants submitted the foreign priority document Cuban Patent Application No. 166/2001, filed on July 12, 2001, however Applicants noted with the foreign document submission dated April 5, 2002, that the Cuban Patent Office has changed the serial number of this Cuban Patent Application from 166/2001 to 167/2001 and Applicants stated: "It is planned to file a substitute

declaration to reflect this change." It is noted that no substitute declaration has been submitted to reflect this change. Appropriate correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1, 3-11, 27, and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 5,788,985, Rodriguez et al., issued 8/4/98 (IDS), in view of Estevez et al (Vaccine, August 2000, 18:190-197), US Patent 4,857,637, Hammonds et al., issued 8/15/89 and Udayachander et al (Human Antibodies, 1997, 8:60-64).

The claims are drawn to a pharmaceutical composition that potentiates immunogenicity of low immunogenic antigens comprising (s) one or more low immunogenic antigens, wherein the low immunogenic antigen is a polypeptide and (b) a vaccine carrier consisting of very small size proteoliposomes (VSSPs), wherein the VSSPs are derived from the Outer Membrane Protein Complex (OMPC) of *Neisseria meningitides* wherein gangliosides have been incorporated into the OMPC, wherein the pharmaceutical composition stimulates both humoral and cellular responses against the antigen (claim 1), wherein the low immunogenic antigen is a growth factor receptor (claim 3), wherein the extra-cellular domains of the growth factor receptor may or may not contain the trans-membrane region (claim 4), wherein the growth factor receptor is

HER-1 (claims 5, 29), wherein the *Neisseria meningitides* is either a wild type or genetically modified strain (claim 6), wherein the VSSPs are obtained by hydrophobically incorporating the gangliosides into the OMPC (claim 7), wherein the gangliosides are GM3 or their N-glycolylated variations (claim 8), wherein the adjuvant is an oily adjuvant and is Incomplete Freund's Adjuvant (claims 9 and 10), the composition of claim 10 wherein the Incomplete Freund's adjuvant is Montanide ISA 51 (claim 11), and the composition of claim 1 wherein the composition further comprises one or more adjuvants (claim 27).

US Patent 5,788,985 teaches a pharmaceutical composition comprising an Outer Membrane Protein Complex (OMPC) of *Neisseria meningitides* wherein gangliosides have been incorporated into the OMPC (Examples 2-4). US Patent 5,788,985 teaches that the pharmaceutical composition increases the immune response against N-glycolylated ganglioside, especially N-glycol GM3 (NGcGM3), which can be used for the treatment of cancer (col. 1, lines 1-12), especially breast cancer which has a higher expression of gangliosides GM3 and GD3 compared to normal breast tissue (abstract; col. 1, lines 59-63 and Example 6), hence gangliosides are targets in treatment approaches (col. 1, lines 64-66). US Patent 5,788,985 teaches the incorporation of gangliosides, including the hydrophobic incorporation of NGcGM3, into the OMPC (col. 2, lines 30-36; col. 3, lines 1-20; Example 2), wherein the *N. meningitides* would be expected to be a wild-type strain (col. 6, lines 1-3).

US Patent 5,788,985 does not teach the pharmaceutical composition further comprising the low immunogenic antigen HER-1 or Incomplete Freund's adjuvant (IFA),

wherein the IFA is Montanide ISA 51, and wherein the pharmaceutical composition stimulates both humoral and cellular responses against HER-1 antigen.

Estevez et al teach that immunization using VSSPs derived from the OMPC of *Neisseria meningitides* with gangliosides incorporated into the OMPC, resulted in significant levels of T-dependent IgG1, IgG2a and IgG2b (cellular) as well as T-independent IgG3 and IgM (humoral) immune responses, wherein no reactogenicity was observed when self-gangliosides were used for immunization. VSSP overcame natural tolerance to the low-immunogenic self-antigen gangliosides in an adjuvant-dependent fashion (abstract; p. 196, col. 1; Fig. 4). It is known that serotype proteins, which are the main components of the OMPC, induce proliferation and activation of lymphocytes and lead to secretion of IL-2 (p. 196, 1st column, last paragraph to 2nd column). Estevez et al teach immunization using Incomplete Freund's Adjuvant Montanide ISA 51 with the VSSPs derived from the OMPC of *Neisseria meningitides* and gangliosides incorporated into the OMPC (p. 191, col. 2; Table 1; Fig. 4 and 7). Estevez et al teach that Montanide ISA 51 is preferred because it is less toxic than Incomplete Freund's Adjuvant (p. 191, col. 2). Immunization of mice with VSSPs derived from the OMPC of *Neisseria meningitides* and gangliosides incorporated into the OMPC in combination with Montanide ISA 51 resulted in increased immunoglobulin titers compared to mice immunized with the VSSP composition without Montanide ISA 51 (p. 194, col. 2; Table 1). Estevez et al teach that patients suffering from metastatic breast cancer have been immunized with GM3/VSSP and NGcGM3/VSSP vaccines in Montanide ISA 51 for therapy (p. 196, col. 2).

US Patent 4,857,637 teaches a pharmaceutical composition comprising the polypeptide epidermal growth factor receptor (EGFR, also known as HER-1) as an antigen to immunize animals against the EGFR (col. 3, lines 36-43; col. 4, lines 58-63). US Patent 4,857,637 teaches that EGFR is overexpressed in malignant cells and is a desirable target for therapy (col. 3, lines 63-66; col. 4, lines 26-38). Immunization may comprise administering growth factor receptor derivatives or intact receptors (col. 4, lines 57-61). Growth factor receptors comprise extracellular, transmembrane and cytoplasmic domains, wherein immunization of a receptor comprising the extracellular domain is desirable because the extracellular domain is accessible to antibodies under *in vivo* conditions, unlike the intracellular or cytoplasmic domains (col. 8, lines 47-68). US Patent 4,857,637 teaches the immunization of growth factor receptors with an adjuvant, such as Incomplete Freund's, because poorly immunogenic proteins are rendered more immunogenic by the use of adjuvants (col. 4, lines 63-68; col. 5, lines 50-55; col. 7, lines 1-3; col. 18, lines 50-55).

Udayachander et al teach that many malignancies, such as breast cancer, overexpress EGFR and EGFR is a target for therapy (abstract).

These references suggest the importance of each of the claimed pharmaceutical composition components in stimulating an immune response to the ganglioside or EGFR antigen. However, the references are deficient in that they do not teach using these components together. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the Outer Membrane Protein Complex (OMPC) of *Neisseria meningitides* wherein ganglioside antigens have been

incorporated into the OMPC taught by US Patent 5,788,985 and Estevez et al, and the EGFR (HER-1) antigen taught by US Patent 4,857,637 in combination in order to treat malignant tumors that overexpress these two antigens, such as breast cancer, because US Patent 5,788,985 teaches that breast cancer overexpresses ganglioside GM3 and Udayachander et al teach that breast cancer overexpresses HER-1. One of ordinary skill in the art would have been motivated to use the two pharmaceutical components in combination in a method of treating a malignant tumor that overexpresses the two antigens, such as breast cancer, in view of the importance of targeting these two antigens for cancer therapy. Each of these agents had been taught by the prior art to be therapeutic targets in the treatment of malignant tumors, such as breast cancer, thus the instant situation is amenable to the type of analysis set forth in In re Kerkhoven, 205 USPQ 1069 (CCPA 1980) wherein the court held that it is *prima facie* obvious to combine two modes of treatment, each of which is taught by the prior art to be useful for the same purpose in order to make a protocol that is to be used for the very same purpose since the idea of combining them flows logically from their having been individually taught in the prior art. One of ordinary skill in the art would have reasonably expected to obtain effective therapeutic targeting of malignant tumors, such as breast cancer, with either or both of these agents since both had been demonstrated in the prior art to successfully illicit an immune response specific to the target cancer antigen.

Similarly, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use Incomplete Freund's adjuvant (IFA) or the IFA Montanide ISA 51 in addition to the two pharmaceutical components because

adjuvant is conventionally used in pharmaceutical compositions, US Patent 4,857,637 teaches that poorly immunogenic proteins are rendered more immunogenic by the use of adjuvants such as IFA, and Estevez et al demonstrate Montanide ISA 51 increases antibody production. One would have been motivated to add IFA or Montanide ISA 51 to the pharmaceutical composition taught by the combined references in order to boost the immune response to the antigens for therapeutic purposes.

Although the references do not teach that the composition stimulates both humoral and cellular responses against the HER-1 (EGFR) antigen Estevez et al teach that VSSPs derived from the OMPC of *Neisseria meningitides* are known to induce humoral and cellular immune responses against low-immunogenic self-antigens in an adjuvant-dependent fashion. Hence, the composition taught by the prior art would necessarily induce both a humoral and cellular immune response against a low immunogenic antigen such as HER-1.

Relevant Arguments

5. Applicants argue that there is no disclosure in US Patent 5,788,985 (Rodriguez et al) that the VSSPs can be utilized to potentiate the immunogenicity of low immunogenic antigens, such as growth factor receptors and there is no disclosure in any secondary references that the VSSPs of Rodriguez et al that the immunogenicity of low immunogenic antigens, such as growth factor receptors, could be potentiated, and there is no motivation to combine the references as proposed by the Examiner. Applicants argue that in the absence of any teaching in the primary or secondary

references concerning the potentiation of the immunogenicity of growth factor receptors, there is no motivation or suggestion in the cited art to combine these references in the manner proposed by the Examiner. Applicants argue that Examiner did not address where the motivation to combine could be found in the cited references or within the general skill in the art, particularly in light of the lack of any teaching in the cited prior art of the adjuvant property off the VSSPs (p. 6).

The arguments have been considered but are not found persuasive. Examiner's motivation to combine references is stated clearly in the rejection above: "One of ordinary skill in the art would have been motivated to use the two pharmaceutical components in combination in a method of treating a malignant tumor that overexpresses the two antigens, such as breast cancer, in view of the importance of targeting these two antigens for cancer therapy. Each of these agents had been taught by the prior art to be therapeutic targets in the treatment of malignant tumors, such as breast cancer, thus the instant situation is amenable to the type of analysis set forth in In re Kerkhoven, 205 USPQ 1069 (CCPA 1980) wherein the court held that it is *prima facie* obvious to combine two modes of treatment, each of which is taught by the prior art to be useful for the same purpose in order to make a protocol that is to be used for the very same purpose since the idea of combining them flows logically from their having been individually taught in the prior art. One of ordinary skill in the art would have reasonably expected to obtain effective therapeutic targeting of malignant tumors, such as breast cancer, with either or both of these agents since both had been demonstrated in the prior art to successfully illicit an immune response specific to the

target cancer antigen." Examiner's motivation to combine does not have to be the same as Applicants' motivation to combine. MPEP 2144 states: "The reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant. In re Linter, 458 F.2d 1013, 173 USPQ 560 (CCPA 1972) (discussed below); In re Dillon, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1990), cert. denied, 500 U.S. 904 (1991) (discussed below). Although Ex parte Levengood, 28 USPQ2d 1300, 1302 (Bd. Pat. App. & Inter. 1993) states that obviousness cannot be established by combining references "without also providing evidence of the motivating force which would impel one skilled in the art to do what the patent applicant has done" (emphasis added), reading the quotation in context it is clear that while there must be motivation to make the claimed invention, there is no requirement that the prior art provide the same reason as the applicant to make the claimed invention."

Further, contrary to Applicants' statement, the art does teach the adjuvant property of VSSPs for poorly immunogenic antigens and that this was a known characteristic of VSSPs. As stated in the above rejection: "Estevez et al teach that immunization using VSSPs derived from the OMPC of *Neisseria meningitides* with gangliosides incorporated into the OMPC, resulted in significant levels of T-dependent IgG1, IgG2a and IgG2b (cellular) as well as T-independent IgG3 and IgM (humoral) immune responses, wherein no reactogenicity was observed when self-gangliosides were used for immunization. VSSP overcame natural tolerance to the low-immunogenic

self-antigen gangliosides in an adjuvant-dependent fashion (abstract; p. 196, col. 1; Fig. 4). It is known that serotype proteins, which are the main components of the OMPC, induce proliferation and activation of lymphocytes and lead to secretion of IL-2 (p. 196, 1st column, last paragraph to 2nd column)".

Finally, with regards to the composition taught by the combined references potentiating the immunogenicity of low immunogenic antigens such as growth factor receptors (HER-1), the rejection above addresses this argument: "Although the references do not teach that the composition stimulates both humoral and cellular responses against the HER-1 (EGFR) antigen Estevez et al teach that VSSPs derived from the OMPC of *Neisseria meningitides* are known to induce humoral and cellular immune responses against low-immunogenic self-antigens. Hence, the composition taught by the prior art would necessarily induce both a humoral and cellular immune response against a low immunogenic antigen such as HER-1".

6. Applicants reiterate the argument that that there is no disclosure in Rodriguez et al that the VSSPs can be used as a carrier, i.e., and adjuvant to potentiate, i.e., increase the immunogenicity of low immunogenic antigens that are polypeptides. The combination of Rodriguez et al and Hammonds et al is simply the combination of two antigens in a vaccine composition. There is no disclosure in either reference alone or together that VSSPs can act as a carrier, i.e., and adjuvant, to potentiate the immune response against a low immunogenic peptide antigen. Applicants argue that because there is no such disclosure in these references, there is no disclosure that an

immunogenic potentiating effective amount of the VSSPs should be used in the composition. Applicants argue there is no disclosure in the references that the composition stimulates both a humoral and cellular response against the low immunogenic peptide antigen, thus Applicants submit that the Examiner's combination of references does not render obvious the claimed subject matter (p. 7).

The arguments have been considered but are not found persuasive. Both agents of the claimed pharmaceutical composition were taught in the prior are to be used for the same purpose of treating breast cancer. The motivation to combine the two agents has already been addressed above. VSSPs were already known in the art to potentiate the immunogenicity of low immunogenic antigens and to stimulate both humoral and cellular immune responses as addressed above. The pharmaceutical composition taught by the combined references would necessarily induce both a humoral and cellular immune response against a low immunogenic antigen such as HER-1 for the reasons set forth above.

7. Applicants argue that they have surprisingly found that the claimed pharmaceutical composition of the present invention confers immunogenicity to the polypeptides by mixing them with VSSPs such as described by Rodriguez et al. Applicants argue that the use of VSSPs as an adjuvant (carrier) is not disclosed in Rodriquez et al or in the secondary references. (p. 7).

The arguments have been considered but are not found persuasive. VSSPs were already known in the art to potentiate the immunogenicity of low immunogenic antigens

and to stimulate both humoral and cellular immune responses as addressed above, hence this is not a "surprising" effect as argued by Applicants. The immunogenicity conferred to a low immunogenic peptide by VSSPs is not surprising and was already known in the art before the time of filing. Further, the art (Livingston et al, Vaccine, 1993, 11:1199-1204) teach that preparations comprising the highly hydrophobic outer membrane proteins (OMP) of *Neisseria meningitides* naturally form liposome-like multi-molecular vesicular structures that readily incorporate antigens and are referred to as "proteosomes." Proteosomes are considered potential adjuvants since OMP are potent T-cell-dependent antigens and B-cell mitogens. They have been shown to initiate and augment IgG antibody responses against peptides when hydrophobically complexed to them via lipid moieties present in the peptide's amino or carboxyl terminus. Livingston et al identify proteosomes as a particularly potent adjuvant for immunization against ganglioside GD3 (p. 1200, col. 1). Levi et al (Vaccine, 1995, 13:1353-1359) teach that proteosomes prepared from *Neisseria meningitides* with influenza peptide antigens hydrophobically incorporated generated both humoral and cellular immune responses to the antigens (abstract, p. 1353, col. 1; p. 1354, col. 1-2; p. 1357, col. 1). Levi et al describe proteosomes as a carrier and adjuvant for peptide-based vaccines and teach that this system could be used to incorporate different peptides (p. 1357, col. 1; p. 1358, col. 1).

The rejection above addresses Applicants' arguments with regards to VSSPs acting as an adjuvant (carrier) (see Estevez et al above).

8. Applicants continue to argue that the claimed pharmaceutical composition shows surprising immunological properties such as the dramatic ability to cause dendritic cell maturation and restoring immune-suppressed patients. Moreover, the claimed composition has the capacity of stimulating both humoral and cellular responses against a particular low immunogenic antigen. Applicants amended the claims to include this latter limitation. Applicants argue this limitation is not disclosed or suggested in the prior art references. Applicants reiterate previous arguments and argue that two main features distinguish the present invention from the cited prior art: (1) the rather small size of the particles in VSSP and (2) the biological functions of the ganglioside.

Applicants summarize methods in the art used to improve the immunogenicity of antigens (p. 9-10). Applicants argue that Hammonds et al had the aim of inducing an autoiummune response and argue that Hammonds et al require that the polypeptides should be foreign or heterologous to the animal species being immunized. Applicants argue that the present invention discloses a composition with adjuvant properties which stimulates the immunogenicity of polypeptides. Applicants argue that this feature of VSSPs has not been anticipated or suggested by any of the prior art (p. 11).

The arguments have been considered but are not found persuasive. Hammonds et al does not require that the polypeptides should be foreign or heterologous to the animal species being immunized as Applicants assert and Applicants have not specifically pointed to this requirement in the Hammonds et al patent. Hammonds et al clearly teaches using HER-1 protein, especially in combination with an adjuvant, to elicit an immune response against HER-1 to treat breast cancer as stated in the above

rejection. The combined references make obvious the claimed composition for the reasons set forth above. The adjuvant properties of VSSPs were known in the art as addressed above.

9. Applicants reiterate arguments that the present invention intended not only an antibody response by means of the agonist and antagonist of the growth factor receptor but also to stimulate the whole immune system of the animal or human being, i.e., both a humoral and a cellular response as set forth in the claims. The present invention provides evidence that the relative superiority of VSSP as adjuvant for different antigen variants, including a model of the HER-1 extracellular domain protein. Applicants submit several publications demonstrating stimulation of humoral and/or cellular responses to antigens using VSSPs (p. 11-12). Applicants argue that the objective evidence provided in the numerous examples in the present application as well as the objective evidence in the publications presented clearly establishes the surprising and unexpected adjuvant property of the claimed VSSPs, i.e., VSSPs derived from the OMPC of *Neisseria meningitides* wherein gangliosides have been incorporated into the OMPC, and the corresponding surprising and unexpected property that the VSSPs are able to potentiate the immunogenicity of low immunogenic antigens that are polypeptides. Applicants reiterate arguments that the objective evidence further demonstrates the surprising and unexpected property that the claimed composition containing the specified low immunogenic antigens and the VSSPs stimulates both the humoral and

cellular immune responses. Applicants argue that neither of these properties is taught or suggested by the cited prior art (p. 12-13).

The arguments have been considered but are not found persuasive for the reasons set forth above. The adjuvant property of the VSSPs, especially to stimulate a humoral and cellular response for a low immunogenic antigen, were already known in the art and are not surprising or unexpected. As stated in the above rejection: "Although the references do not teach that the composition stimulates both humoral and cellular responses against the HER-1 (EGFR) antigen, Estevez et al teach that VSSPs derived from the OMPC of *Neisseria meningitides* are known to induce humoral and cellular immune responses against low-immunogenic self-antigens in an adjuvant-dependent fashion. Hence, the composition taught by the prior art would necessarily induce both a humoral and cellular immune response against a low immunogenic antigen such as HER-1". The combined references render obvious the instantly claimed composition for the reasons set forth above.

10. Claims 1, 3-11, 27-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 6,149,921, Rodriguez et al, filed 4/17/1998, issued 11/21/2000 (IDS), in view of Estevez et al (Vaccine, August 2000, 18:190-197), US Patent 4,857,637, Hammonds et al., issued 8/15/89 and Udayachander et al (Human Antibodies, 1997, 8:60-64).

The claims are drawn to a pharmaceutical composition that potentiates immunogenicity of low immunogenic antigens comprising (s) one or more low immunogenic antigens, wherein the low immunogenic antigen is a polypeptide and (b) a vaccine carrier consisting of very small size proteoliposomes (VSSPs), wherein the VSSPs are derived from the Outer Membrane Protein Complex (OMPC) of *Neisseria meningitides* wherein gangliosides have been incorporated into the OMPC, wherein the pharmaceutical composition stimulates both humoral and cellular responses against the antigen (claim 1), wherein the low immunogenic antigen is a growth factor receptor (claim 3), wherein the extra-cellular domains of the growth factor receptor may or may not contain the trans-membrane region (claim 4), wherein the growth factor receptor is HER-1 (claims 5, 29), wherein the *Neisseria meningitides* is either a wild type or genetically modified strain (claim 6), wherein the VSSPs are obtained by hydrophobically incorporating the gangliosides into the OMPC (claim 7), wherein the gangliosides are GM3 or their N-acetylated or N-glycolylated variations (claim 8), wherein the adjuvant is an oily adjuvant and is Incomplete Freund's Adjuvant (claims 9 and 10), the composition of claim 10 wherein the Incomplete Freund's adjuvant is Montanide ISA 51 (claim 11), and the composition of claim 1 wherein the composition further comprises one or more adjuvants (claim 27), the composition of claim 8 wherein the gangliosides are N-acetylated GM3 (claim 28).

US Patent 6,149,921 teaches a pharmaceutical composition comprising either N-glycolylated GM3 (NGcGM3) or N-acetylated GM3 (NAcGM3) gangliosides hydrophobically incorporated into the OMPC of *Neisseria meningitides*, wherein the

composition can be combined with a selection of adjuvants including Freund's Incomplete Adjuvant Montanide ISA 51 (col. 3, lines 15-67; col. 5, lines 14-22; col. 5, line 65 through col. 6, line 6; Example 7; Claims). NGcGM3 and NAcGM3 are antigens which are both present in breast tumors and the pharmaceutical composition comprising these gangliosides can be used to augment an immune response in an animal and for treating cancer (col. 2, lines 63-67; col. 3, lines 45-67). These compositions may be used in the treatment of breast cancers, whereby gangliosides are used to elicit an immune response to corresponding gangliosides on breast tumor cells (abstract). The *N. meningitides* would be expected to be a wild-type strain (col. 6, lines 49-52; col. 7, lines 3-5).

US Patent 6,149,921 does not teach the N-glycolylated or N-acetylated GM3 gangliosides hydrophobically incorporated into the OMPC of *Neisseria meningitides* in combination with a low immunogenic antigen that is HER-1, that stimulates both humoral and cellular responses against the antigen.

Estevez et al teach that immunization using VSSPs derived from the OMPC of *Neisseria meningitides* with gangliosides incorporated into the OMPC, resulted in significant levels of T-dependent IgG1, IgG2a and IgG2b (cellular) as well as T-independent IgG3 and IgM (humoral) immune responses, wherein no reactogenicity was observed when self-gangliosides were used for immunization. VSSP overcame natural tolerance to the low-immunogenic self-antigen gangliosides in an adjuvant-dependent fashion (abstract; p. 196, col. 1; Fig. 4). It is known that serotype proteins, which are the main components of the OMPC, induce proliferation and activation of

lymphocytes and lead to secretion of IL-2 (p. 196, 1st column, last paragraph to 2nd column). Estevez et al teach immunization using Incomplete Freund's Adjuvant Montanide ISA 51 with the VSSPs derived from the OMPC of *Neisseria meningitides* and gangliosides incorporated into the OMPC (p. 191, col. 2; Table 1; Fig. 4 and 7). Estevez et al teach that Montanide ISA 51 is preferred because it is less toxic than Incomplete Freund's Adjuvant (p. 191, col. 2). Immunization of mice with VSSPs derived from the OMPC of *Neisseria meningitides* and gangliosides incorporated into the OMPC in combination with Montanide ISA 51 resulted in increased immunoglobulin titers compared to mice immunized with the VSSP composition without Montanide ISA 51 (p. 194, col. 2; Table 1). Estevez et al teach that patients suffering from metastatic breast cancer have been immunized with GM3/VSSP and NGcGM3/VSSP vaccines in Montanide ISA 51 for therapy (p. 196, col. 2).

US Patent 4,857,637 teaches a pharmaceutical composition comprising the polypeptide epidermal growth factor receptor (EGFR, also known as HER-1) as an antigen to immunize animals against the EGFR (col. 3, lines 36-43; col. 4, lines 58-63). US Patent 4,857,637 teaches that EGFR is overexpressed in malignant cells and is a desirable target for therapy (col. 3, lines 63-66; col. 4, lines 26-38). Immunization may comprise administering growth factor receptor derivatives or intact receptors (col. 4, lines 57-61). Growth factor receptors comprise extracellular, transmembrane and cytoplasmic domains, wherein immunization of a receptor comprising the extracellular domain is desirable because the extracellular domain is accessible to antibodies under *in vivo* conditions, unlike the intracellular or cytoplasmic domains (col. 8, lines 47-68).

US Patent 4,857,637 teaches the immunization of growth factor receptors with an adjuvant, such as Incomplete Freund's, because poorly immunogenic proteins are rendered more immunogenic by the use of adjuvants (col. 4, lines 63-68; col. 5, lines 50-55; col. 7, lines 1-3; col. 18, lines 50-55).

Udayachander et al teach that many malignancies, such as breast cancer, overexpress EGFR and EGFR is a target for therapy (abstract).

These references suggest the importance of each of the claimed pharmaceutical composition components in stimulating an immune response to the ganglioside or EGFR antigen. However, the references are deficient in that they do not teach using these components together. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the Outer Membrane Protein Complex (OMPC) of *Neisseria meningitides* wherein ganglioside antigens have been incorporated into the OMPC taught by US Patent 6,149,921 and Estevez et al, and the EGFR (HER-1) antigen taught by US Patent 4,857,637 in combination in order to treat malignant tumors that overexpress these two antigens, such as breast cancer, because US Patent 6,149,9215 teaches that breast cancer expresses antigen gangliosides NAcGM3 and NGcGM3 and Udayachander et al teach that breast cancer overexpresses HER-1. One of ordinary skill in the art would have been motivated to use the two pharmaceutical components in combination in a method of treating a malignant tumor that expresses the two antigens, such as breast cancer, in view of the importance of targeting these two antigens for cancer therapy. Each of these agents had been taught by the prior art to be therapeutic targets in the treatment of malignant

tumors, such as breast cancer, thus the instant situation is amenable to the type of analysis set forth in In re Kerkhoven, 205 USPQ 1069 (CCPA 1980) wherein the court held that it is *prima facie* obvious to combine two modes of treatment, each of which is taught by the prior art to be useful for the same purpose in order to make a protocol that is to be used for the very same purpose since the idea of combining them flows logically from their having been individually taught in the prior art. One of ordinary skill in the art would have reasonably expected to obtain effective therapeutic targeting of malignant tumors, such as breast cancer, with either or both of these agents since both had been demonstrated in the prior art to successfully illicit an immune response specific to the target cancer antigen.

Although the references do not teach that the composition stimulates both humoral and cellular responses against the HER-1 (EGFR) antigen Estevez et al teach that VSSPs derived from the OMPC of *Neisseria meningitides* are known to induce humoral and cellular immune responses against low-immunogenic self-antigens in an adjuvant-dependent fashion. Hence, the composition taught by the prior art would necessarily induce both a humoral and cellular immune response against a low immunogenic antigen such as HER-1.

Relevant Arguments

11. Applicants state that N-glycolylated gangliosides, including GM3, are present in most species (mice, rats, dogs, horses, pigs, etc) but not humans and chickens. In

contrast the gangliosides in claim 28 are N-acetylated GM3 which is more abundant in extra neural tissues. Applicants state that the results of immunizing human beings with either ganglioside will be different because of the amount of normal expression of each ganglioside in the human. Applicants argue that compositions containing VSSPs containing N-acetylated gangliosides is not obvious from the cited references because N-acetylated gangliosides are "self-antigens" and are much less immunogenic than N-glycolylated antigens which would be "foreign" antigens (p. 13).

The arguments have been considered but are not found persuasive. The rejection above, based on primary reference US Patent 6,149,921, addresses Applicants' arguments regarding the obviousness of using N-acetylated GM3 in the claimed composition. Contrary to Applicants' assertion that N-glycolylated GM3 gangliosides are not present in chickens and humans, Estevez et al (above) states that N-glycolylated GM3 is indeed present in chickens, hence would not be a "foreign" antigen (p. 194, col. 1, last paragraph) and both US Patents 6,149,921 and 5,788,985 (above) teach that N-glycolylated GM3 (NGcGM3) is expressed in human breast tumors, hence is not a "foreign" antigen ('921: col. 2, lines 63-67; col. 3, lines 45-50; '985: col. 1, lines 50-67).

12. All other rejections recited in the Office Action mailed 12/18/2006 are hereby withdrawn.

13. **Conclusion:** No claim is allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura B. Goddard, Ph.D. whose telephone number is (571) 272-8788. The examiner can normally be reached on 7:00am-3:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Examiner
Art Unit 1642